

Pharmaceutical formulation for the active ingredient
budesonide

Field of the invention

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The invention relates to a pharmaceutical formulation for the active ingredient budesonide

Prior art

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Löfberg, R. describes in "Research and Clinical Forums, Vol. 15 (5), pages 92-96 (1993), budesonide formulations for oral therapy of "inflammatory bowel disease (IBD)". Described therein are budesonide pellets consisting of a sugar core with a thin budesonide layer in an undefined, water-insoluble rate limiting polymer and a coating of Eudragit® L 100-55. The pellets can be packed into gelatin capsules which represent the actual pharmaceutical form.

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WO 95/08323 describes budesonide pellets with controlled release profile and a process for producing them. To improve the solubility of budesonide, the active ingredient is applied to the pellet cores in a mixture of excipients. For this purpose, the active ingredient is suspended in an alcohol:water mixture of 0:100 to 20:80, and at least two parts of a suitable water-soluble excipient, e.g. α -lactose monohydrate, sucrose or monosodium citrate, are added to one part of the mixture. In order to obtain a suitable release profile, the budesonide cores are coated with a two-layer coating of, for example, Eudragit® L, S, RS and/or RL inside and Eudragit® RS/RL outside.

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WO 97/00512 and US 5,849,327 describe pharmaceutical forms for release of active ingredients such as, for example, budesonide in the lower gastrointestinal tract. The pharmaceutical form comprises the active

ingredient bound in crosslinked polymer particles which are additionally coated with Eudragit® 100 S (copolymer of methyl methacrylate and methacrylic acid) a micro-bially degradable polysaccharide. The particles are
5 packed into capsules which may, for example, in turn be coated with Eudragit® 100 S.

WO 01/68058 relates to the use of a multilayer pharmaceutical form which is essentially composed of a)
10 a core with an active pharmaceutical ingredient which may be, for example, budesonide, b) an inner coating of a copolymer or a mixture of copolymers which are composed of 85 to 98% by weight free-radical polymerized C1- to C4-alkyl esters of acrylic or methacrylic acid and 15
15 to 2% by weight (meth)acrylate monomers with a quaternary ammonium group in the alkyl radical, and c) an outer coating of a copolymer which is composed of 75 to 95% by weight free-radical polymerized C1- to C4-alkyl esters of acrylic or methacrylic acid and 5 to
20 25% by weight (meth)acrylate monomers with an anionic group in the alkyl radical, for producing a pharmaceutical form which in the USP release test for two hours at pH 1.2 and subsequent rebuffering to pH 7.0 releases the contained active ingredient to the
25 extent of less than 5% in the period up to 2.0 hours after the start of the test and to the extent of 30 to 80% at the time eight hours after the start of the test. The outer coating may be of the Eudragit® FS type.

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Object and achievement

One problem with pharmaceutical formulations containing the active ingredient budesonide is the low solubility
35 of the active ingredient. One way of improving the solubility is, according to WO 95/08323, to formulate budesonide using water-soluble excipients.

For this purpose it is necessary to suspend budesonide

in an alcohol:water mixture of 0:100 to 20:80. This is regarded as disadvantageous because, at present, because of environmental and occupational safety considerations, avoidance of the use of organic solvents is always attempted.

In addition, the formulation must take place with water-soluble excipients, e.g. α -lactose monohydrate, sucrose or monosodium citrate, which may lead to unwanted side effects. A known example is lactose intolerance in patients suffering from bowel diseases such as ulcerative colitis.

One object was regarded as being the provision of a budesonide formulation which avoids the prior art disadvantages. The production is intended to be possible entirely without the use of organic solvents. Excipients for increasing the solubility, like those mentioned in WO 95/08323, should be substantially avoided in order to reduce the risk of intolerance.

The object is achieved by a pharmaceutical formulation substantially comprising

a) an inner layer, which may where appropriate be applied to a core, with the active ingredient budesonide, bound in a binder

b) an intermediate layer with a polymeric coating agent which is soluble in intestinal juice or extends release,

c) an outer envelope which is resistant to gastric juice or an outer layer with a coating agent which is resistant to gastric juice

where the layers may comprise in a manner known per se further pharmaceutically usual excipients,

characterized in that

the binder is a polymer or copolymer with acidic
5 groups, and the formulation of the inner layer without
intermediate and outer layer releases the bound active
ingredient in the release test according to USP XXIII
monograph <711> "Dissolution" with apparatus 2 (paddle)
with 100 revolutions/min in phosphate buffer of pH 7.5
10 (according to monograph "Intestinal Fluid, Simulated,
TS" without addition of pepsin) to the extent of more
than 80% after 30 min.

Mode of operation of the invention

15 The pharmaceutical formulation according to the
invention substantially comprises

a) an inner layer, which may where appropriate be
20 applied to a core, with the active ingredient
budesonide, bound in a binder

b) an intermediate layer with a polymeric coating agent
which is soluble in intestinal juice or extends
25 release,

c) an outer envelope which is resistant to gastric
juice or an outer layer with a coating agent which is
resistant to gastric juice
30

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further pharmaceutically usual excipients,

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groups, and the formulation of the inner layer without
intermediate and outer layer releases the bound active
ingredient in the release test according to USP XXIII

monograph <711> "Dissolution" with apparatus 2 (paddle) with 100 revolutions/min in phosphate buffer of pH 7.5 (according to monograph "Intestinal Fluid, Simulated, TS" without addition of pepsin) to the extent of more than 80% after 30 min.

Inner layer a)

The inner layer, which may where appropriate be applied to a core, comprises the active ingredient budesonide, bound in a polymeric binder with acidic groups.

The active ingredient budesonide is preferably employed in the commercially available micronized form. The average particle size may be, for example, in the range from 2 to 50 μm , preferably 5 to 25 μm , in particular 8 to 15 μm .

The active ingredient budesonide is bound in a polymeric binder with acidic groups. The binding of the active ingredient in the polymeric binder is intended preferably to take place without the use of organic solvents.

The polymeric binder with acidic groups may be, for example, a water-soluble polymer which can be applied in the form of a dispersion together with the active ingredient and, where appropriate, further excipients for example by spray application. It is possible in this way for example to provide pellets with an active ingredient-containing budesonide coating.

The polymeric binder with acidic groups may also be for example a polymer which can be thermally plasticated and which is melted in the presence of the active ingredient and, where appropriate, further excipients, or into a melt of which the active ingredient and, where appropriate, the further excipients are put. It is possible for example to produce active ingredient-

containing sheets and to seal cores therein, or to apply the formulation of layer a) by spray application in the molten state.

- 5 Processing in this case can take place for example by injection molding or extrusion. The mixture can be converted into the form of granules for example by hot cut.

10 **Polymeric binder with acidic groups**

Any pharmaceutically usable polymeric binder with acidic groups which, in combination with the bound active ingredient, leads to release of more than 80% of
15 the bound budesonide after 30 min in the release test according to USP XXIII monograph <711> "Dissolution" with apparatus 2 (paddle) at 100 revolutions/min in phosphate buffer of pH 7.5 according to monograph "Intestinal Fluid, Simulated, TS" without addition of
20 pepsin, is suitable for the purposes of the invention. This is possible only if there is an interaction between polymeric binders with acidic groups and the budesonide which increase the solubility of the budesonide. The exact molecular mechanism of the
25 increase in solubility in this connection is unknown. It is merely assumed that the acidic groups are involved therein.

Those particularly suitable are

- 30 polymeric binders which are (meth)acrylate copolymers which comprise 40 to 95% by weight free-radical polymerized units of C₁- to C₄-alkyl esters of acrylic or methacrylic acid and 5 to 60% by weight (meth)-
35 acrylate monomers with an anionic group in the alkyl radical. The proportions mentioned can ordinarily add up to 100% by weight. However, it is also possible in addition, without this leading to an impairment or alteration of the essential properties, for small

amounts in the region of 0 to 10, for example 1 to 5,
% by weight of further monomers capable of vinylic
copolymerization, such as, for example, methyl meth-
acrylate, butyl methacrylate, butyl acrylate or
5 hydroxyethyl methacrylate, to be present.

C₁- to C₄-alkyl esters of acrylic or methacrylic acid
are in particular methyl methacrylate, ethyl meth-
acrylate, butyl methacrylate, methyl acrylate, ethyl
10 acrylate and butyl acrylate.

A (meth)acrylate monomer with an anionic group in the
alkyl radical may be for example acrylic acid, but
preferably methacrylic acid. The carboxyl groups may be
15 up to 30 mol%, preferably up to 5 to 15 mol%, partially
neutralized.

Anionic (meth)acrylate copolymers composed of 40 to 60,
% by weight methacrylic acid and 60 to 40% by weight
20 methyl methacrylate or 60 to 40% by weight ethyl
acrylate (Eudragit® L or Eudragit® L 100-55 types) are
suitable.

Equally suitable are anionic (meth)acrylate copolymers
25 composed of 20 to 40% by weight methacrylic acid and 80
to 60% by weight methyl methacrylate (Eudragit® S
type).

Likewise suitable are anionic (meth)acrylate copolymers
30 composed of 20 to 34% by weight methacrylic acid and/or
acrylic acid, 20 to 69% by weight methyl acrylate and 0
to 40% by weight ethyl acrylate and, where appropriate,
0 to 10% by weight further monomers capable of vinylic
copolymerization, with the proviso that the glass
35 transition temperature of the copolymer according to
ISO 11357-2, subsection 3.3.3, is not more than 60°C.
(Eudragit® type with medium methacrylic acid content).

The copolymer is composed in particular of free-radical

polymerized units of

20 to 34, preferably 25 to 33, particularly preferably
28 to 32, % by weight methacrylic acid or acrylic acid,
5 with preference for methacrylic acid,

20 to 69, preferably 35 to 65, particularly preferably
35 to 55, % by weight methyl acrylate and, where
appropriate,

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0 to 40, preferably 5 to 35, particularly preferably 15
to 35, % by weight ethyl acrylate, with the proviso
that the glass transition temperature of the copolymer
(without added plasticizer) according to ISO 11357-2,
15 subsection 3.3.3, is not more than 60, preferably 40 to
60, particularly preferably 45 to 55°C.

The (meth)acrylate copolymer preferably consists
essentially to exclusively of the monomers methacrylic
20 acid, methyl acrylate and ethyl acrylate in the
quantitative proportions indicated above. The propor-
tions mentioned ordinarily add up to 100% by weight.
However, it is also possible in addition, without this
leading to an impairment or alteration of the essential
25 properties, for small amounts in the region of 0 to 10,
for example 1 to 5, % by weight of further monomers
capable of vinylic copolymerization, such as, for
example, methyl methacrylate, butyl methacrylate, butyl
acrylate or hydroxyethyl methacrylate, to be present.

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Said copolymers can be obtained in a manner known per
se by free-radical bulk, solution, bead or emulsion
polymerization. They must be brought before the
processing by suitable grinding, drying or spraying
35 processes into the particle size range according to the
invention.

This can take place by simple crushing of extruded and
cold pellets or hot cut.

The (meth)acrylate copolymer is preferably in the form of a dispersion, e.g. with a water content of from 60 to 80% by weight. The carboxyl groups may be up to 30 mol%, preferably from 5 to 15 mol%, partially
5 neutralized by a base, e.g. NaOH.

Production of the inner layer a) preferably takes place by aqueous spraying of a budesonide-containing (meth)-acrylate copolymer dispersion onto cores, e.g. sucrose
10 pellets, with binding of the budesonide after the evaporation or volatilization of the water. The product temperature during the spray application can be for example 20 to 40, preferably 25 to 35°C. A release agent, e.g. talc, and a plasticizer, e.g. triethyl
15 citrate, are normally added to the budesonide-containing (meth)acrylate copolymer dispersion. The processing of the budesonide and, where appropriate, of the additive can preferably take place by stirring into water with initially vigorous mixing, e.g. by mixing
20 for example with a high-speed mixer (homogenizer) for 5 to 15 minutes. The suspension obtained in this way can then be added to the (meth)acrylate copolymer dispersion. The mixture should expediently be stirred continuously, and preferably also during the spraying
25 process.

Also suitable are

polymeric binders which are vinylpyrrolidone/vinyl
30 acetate copolymers. The molar proportion of vinyl acetate in this case is preferably in a range from 10 to 60 mol%, particularly preferably 30 to 50 mol% (suitable commercial products are, for example, Kollidon® VA64, BASF, Ludwigshafen, Germany).

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However, the vinylpyrrolidone/vinyl acetate copolymers must usually be processed in the form dissolved a solvent, e.g. ethanol, which is less preferred.

Production of the inner layer a) can in this case take place by spraying a budesonide-containing vinylpyrrolidone/vinyl acetate copolymer solution, e.g. in ethanol, onto cores, e.g. sucrose pellets, with binding of the budesonide after evaporation of the solvent. The spraying temperature can in this case be for example from 30 to 60°C. A release agent, e.g. talc, and a plasticizer, e.g. triethyl citrate, are normally added to budesonide-containing vinylpyrrolidone/vinyl acetate copolymer solution.

Intermediate layer b)

The intermediate layer consists essentially of a polymeric coating agent which is soluble in intestinal juice or extends release.

Polymeric coating agents which are soluble in intestinal juice

Suitable examples are (meth)acrylate copolymers which comprise 40 to 100% by weight free-radical polymerized units of C₁- to C₄-alkyl esters of acrylic or methacrylic acid and no or up to 60% by weight (meth)acrylate monomers with an anionic group in the alkyl radical.

These may be identical to the (meth)acrylate copolymers mentioned above for the inner layer a). The (meth)acrylate copolymers are preferably different from the (meth)acrylate copolymer of the inner layer.

Also suitable in addition are, for example, (meth)acrylate copolymers consisting of 10 to 30% by weight methyl methacrylate, 50 to 70% by weight methyl acrylate and 5 to 15% by weight methacrylic acid (Eudragit® FS type).

Release-extending polymeric coating agents

Release-extending polymeric coating agents are preferably used for the intermediate layer.

5 Suitable examples are (meth)acrylate copolymers which
comprise 85 to 98% by weight free-radical polymerized
units of C1- to C4-alkyl esters of acrylic or
methacrylic acid and 15 to 2% by weight (meth)acrylate
10 radical.

Appropriate (meth)acrylate copolymers are disclosed for
example in EP-A 181 515 or in DE patent 1 617 751. They
are polymers which are soluble or swellable
15 independently of the pH and which are suitable for
pharmaceutical coatings. A possible production method
to be mentioned is bulk polymerization in the presence
of a free-radical initiator dissolved in the monomer
mixture. The polymer can also be produced likewise by
20 solution or precipitation polymerization. The polymer
can be obtained in this way in the form of a fine
powder, achievable in the case of bulk polymerization
by grinding and in the case of solution and precipita-
tion polymerization for example by spray drying.

25 The (meth)acrylate copolymer is composed of 85 to 98%
by weight free-radical polymerized C1- to C4-alkyl
esters of acrylic or methacrylic acid and 15 to 2% by
weight (meth)acrylate monomers with a quaternary
30 ammonium group in the alkyl radical.

Preferred C1- to C4-alkyl esters of acrylic or meth-
acrylic acid are methyl acrylate, ethyl acrylate, butyl
acrylate, butyl methacrylate and methyl methacrylate.

35 The particularly preferred (meth)acrylate monomer with
quaternary ammonium groups is 2-trimethylammoniummethyl
methacrylate chloride.

A corresponding copolymer may be composed for example of 50-70% by weight methyl methacrylate, 20-40% by weight ethyl acrylate and 7-2% by weight 2-trimethylammoniummethyl methacrylate chloride.

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A specifically suitable copolymer comprises 65% by weight methyl methacrylate, 30% by weight ethyl acrylate and 5% by weight 2-trimethylammoniummethyl methacrylate chloride be composed (Eudragit® RS).

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A further suitable (meth)acrylate copolymer may be composed for example of 85 to less than 93% by weight C1- to C4-alkyl esters of acrylic or methacrylic acid and more than 7 to 15% by weight (meth)acrylate monomers with a quaternary ammonium group in the alkyl radical. Such (meth)acrylate monomers are commercially available and have been used for a long time for release-extending coatings.

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20 A specifically suitable copolymer comprises, for example, 60% by weight methyl methacrylate, 30% by weight ethyl acrylate and 10% by weight 2-trimethylammoniummethyl methacrylate chloride (Eudragit® RL).

25 Also suitable in addition are, for example, neutral (meth)acrylate copolymers composed of 20 to 40% by weight ethyl acrylate and 60 to 80% by weight methyl methacrylate (Eudragit® NE type).

30 Blends

The preferred embodiment of layer b) are polymer blends. In particular, the Eudragit® RS 30 D and Eudragit® NE 30 D polymer types with relatively low permeability cause, even in layers of low thickness, a therapeutically unwanted great delay in delivery of active ingredient. For this reason, either the Eudragit® RL polymer type with higher permeability or blends of Eudragit® RL and Eudragit® RS, e.g. in the

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ratio 9:1 to 1:9, are preferably used for layer b). The Eudragit® NE polymer type with pore-forming additions such as, for example, NaCl, sucrose, hydroxypropyl-methylcellulose (HPMC) is also particularly suitable.

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Further polymers

To control delivery of active ingredient it may be advantageous in the individual case to admix further
10 polymers. The content of further polymers in the blend is, however, not more than 20% by weight, preferably not more than 10% by weight, in particular 0-5% by weight, based on the (meth)acrylate copolymer.

15 Examples of such further polymers are: polyvinyl-pyrrolidone, polyvinyl alcohols, anionic (meth)acrylate copolymers composed of methyl methacrylate and/or ethyl
20 acrylate and methacrylic acid (Eudragit® L 100, Eudragit® S 100, Eudragit® L 100-55). Anionic (meth)-acrylate copolymers composed of methyl methacrylate, methyl acrylate and methacrylic acid, carboxymethyl-cellulose salts, hydroxypropylcellulose (HPMC), neutral
25 (meth)acrylate copolymers composed of methyl methacrylate and ethyl acrylate (dry matter from Eudragit® NE 30 D), copolymers of methyl methacrylate and butyl methacrylate (Plastoid® B) or (meth)acrylate copolymers with quaternary ammonium groups (Eudragit® RL and Eudragit® RS).

30 Layer b) usually comprises further pharmaceutically customary excipients

Outer layer c)

35 The outer layer c) may be an outer envelope which is resistant to gastric juice or an outer layer with a coating agent which is resistant to gastric juice. It has the task of preventing premature release of budesonide in the stomach.

Outer envelope which is resistant to gastric juice

5 The outer envelope which is resistant to gastric juice may be a capsule. The capsule preferably consists essentially of gelatin or of hydroxypropylcellulose and be provided in particular with a coating which is resistant to gastric juice.

10 The coating which is resistant to gastric juice of the capsule may be a (meth)acrylate copolymer which comprises 40 to 100% by weight free-radical polymerized units of C₁- to C₄-alkyl esters of acrylic or methacrylic acid and from 5 to 60% by weight (meth)acrylate
15 monomers with an anionic group in the alkyl radical. The (meth)acrylate copolymer for the coating of the capsule may be identical or different from the copolymers of the inner and/or the intermediate layer.

20 The capsules comprise the active ingredient in the form of pellets or granules contains. The pellets or granules accordingly consist of the inner active ingredient-containing layer a) and of the intermediate layer b) which is soluble in intestinal juice or
25 extends release. After the capsule has dissolved in the upper sections of the intestine, the contained pellets or granules are released.

Outer layer c) with a coating agent which is resistant
30 to gastric juice

In place of a filled capsule, a formulation may also be in the form for example of pellets in tablet form.

35 The outer coating agent which is resistant to gastric juice may be a (meth)acrylate copolymer which comprises 40 to 100% by weight free-radical polymerized units of C₁- to C₄-alkyl esters of acrylic or methacrylic acid and from 5 to 60% by weight (meth)acrylate monomers

with an anionic group in the alkyl radical.

5 The (meth)acrylate copolymer may be identical or different from the copolymers of the inner and/or of the intermediate layer. It is preferably different from the (meth)acrylate copolymer of the intermediate layer.

10 Layer c) also usually comprises further customary pharmaceutical excipients.

Core materials:

15 Cores which are optionally employed according to the invention are active ingredient-free pellets or minitabets in the particle size range between 10 to 3000 μm , preferably 100 to 1000 μm . Pellets preferably consist of sucrose, lactose or cellulose and are produced by powder layering or by the wet extrusion process with subsequent spheronization and final
20 drying. Sucrose pellets are preferably employed.

Production of layers b) and c):

25 The production of layers b) and c) takes place by processes customary in pharmaceutical technology, preferably by spray application. However, it is also possible to apply layers b) and c) by melt processing as also for layer a). It is possible for example to produce active ingredient-containing sheets and to seal
30 cores therein, or to apply the layer by spray application in the molten state.

Embodiment based on WO 01/68058

35 An embodiment based on WO 01/68058 is preferred. It is possible in this way to provide a budesonide pharmaceutical form which delivers virtually no active ingredient in the stomach and makes it possible for the active ingredient to be delivered uniformly and long-

term in the intestine, especially shortly before or only in the region of the large intestine. The mode of active ingredient delivery is intended in particular to satisfy the requirement that in the USP release test for two hours at pH 1.2 and subsequent rebuffering to pH 7.0 the release of the contained active ingredient in the period up to 2.0 hours after the start of the test is less than 5% and at the time eight hours after the start of the test is 30 to 80%.

A difference from WO 01/68058 is according to the invention that the inner layer a) is applied to the core which comprises the active ingredient budesonide bound in a polymeric binder with acidic groups. The increased budesonide solubility which is achieved in this way results in an even more advantageous embodiment.

Intermediate layer b) according to WO 01/68058

An intermediate layer b) of a copolymer or a blend of copolymers which are composed of 85 to 98% by weight free-radical polymerized C1- to C4-alkyl esters of acrylic or methacrylic acid and 15 to 2% by weight (meth)acrylate monomers with a quaternary ammonium group in the alkyl radical follows according to WO 01/68058.

A suitable copolymer may be produced for example from 93 to 98% by weight free-radical polymerized C1- to C4-alkyl esters of acrylic or methacrylic acid and 7-2% by weight 2-trimethylammoniummethyl methacrylate chloride. It is moreover possible for example for 50-70% by weight methyl methacrylate, 20-40% by weight ethyl acrylate to be present.

A corresponding copolymer is composed for example of 65% by weight methyl methacrylate, 30% by weight ethyl acrylate and 5% by weight 2-trimethylammoniummethyl

methacrylate chloride (Eudragit® RS).

5 A further suitable copolymer can be produced for example from 85 to less than 93% by weight free-radical polymerized C1- to C4-alkyl esters of acrylic or methacrylic acid and more than 7 to 15% by weight 2-trimethylammoniummethyl methacrylate chloride.

10 A suitable copolymer is composed of 60% by weight methyl methacrylate, 30% by weight ethyl acrylate and 10% by weight 2-trimethylammoniummethyl methacrylate chloride (Eudragit® RL).

15 The proportionate amount of layer b) should be in the range from 2 to 20% by weight based on the core with the active ingredient. It is beneficial to use simultaneously both of the abovementioned copolymer types, preferably those having 5 and having 10% by weight 2-trimethylammoniummethyl methacrylate chloride
20 (Eudragit® RS and Eudragit® RL) in blend. The ratio in the blend can be for example from 20:1 to 1:20, preferably 10:1 to 1:10.

Outer layer c) according to WO 01/68058

25 An outer layer c) of a copolymer which is composed of 75 to 95% by weight free-radical polymerized C₁- to C₄-alkyl esters of acrylic or methacrylic acid and 5 to 60% by weight (meth)acrylate monomers with an anionic
30 group in the alkyl radical follows to produce a pharmaceutical form which in the USP release test for two hours at pH 1.2 and subsequent rebuffering to pH 7.0 releases the contained active ingredient in the period up to 2.0 hours after the start of the test to
35 the extent of less than 5% and at the time eight hours after the start of the test to the extent of 30 to 80%. For the therapy of ulcerative colitis, the outer coating may preferably be of the Eudragit® FS type. For the therapy of Crohn's disease, which may also occur

even in sections of the small intestine, the outer coating may preferably be of the Eudragit® L type. Likewise suitable are anionic (meth)acrylate copolymers composed of 20 to 34% by weight methacrylic acid and/or acrylic acid, 20 to 69% by weight methyl acrylate and 0 to 40% by weight ethyl acrylate and, where appropriate, 0 to 10% by weight further monomers capable of vinylic copolymerization, with the proviso that the glass transition temperature of the copolymer according to ISO 11357-2, subsection 3.3.3, is not more than 60°C. (Eudragit® type with medium methacrylic acid content).

The proportional amount of the outer coating c) should be in the range from 10 to 50% by weight based on the weight of the core with the active ingredient and the inner coating.

Excipients customary in pharmacy

Layers a), b) and c) may comprise further pharmaceutically customary excipients in a manner known per se.

To produce the pharmaceutical form it is possible to employ pharmaceutically customary excipients in a manner known per se. These excipients may be present in the core or in the coating agent.

Dryers (non-stick agents):

Dryers have the following properties: they have large specific surface areas, are chemically inert, are free-flowing and comprise fine particles. Because of these properties, they reduce the tack of polymers containing polar comonomers as functional groups.

Examples of dryers are:

Alumina, magnesium oxide, kaolin, talc, silica (Aerosils), barium sulfate and cellulose.

Release agents

Examples of release agents are:

esters of fatty acids or fatty amides, aliphatic, long-chain carboxylic acids, fatty alcohols and esters thereof, montan waxes or paraffin waxes and metal soaps; particular mention should be made of glycerol monostearate, stearyl alcohol, glycerol behenic acid ester, cetyl alcohol, palmitic acid, canauba wax, beeswax etc. The usual proportionate amounts are in the range from 0.05% by weight to 5, preferably 0.1 to 3, % by weight based on the copolymer.

Further excipients customary in pharmacy:

Mention should be made here of, for example, stabilizers, colorants, antioxidants, wetting agents, pigments, gloss agents etc. They are used in particular as processing aids and are intended can be to ensure a reliable and reproducible production process and good long-term storage stability. Further excipients customary in pharmacy may be present in amounts of from 0.001% by weight to 30% by weight, preferably 0.1 to 10% by weight, based on the copolymer.

Plasticizers:

Substances suitable as plasticizers ordinarily have a molecular weight between 100 and 20 000 and contain one or more hydrophilic groups in the molecule, e.g. hydroxyl, ester or amino groups. Citrates, phthalates, sebacates, castor oil are suitable. Examples of suitable plasticizers are alkyl citrates, propylene glycol, glycerol esters, alkyl phthalates, alkyl sebacates, sucrose esters, sorbitan esters, diethyl sebacate, dibutyl sebacate and polyethylene glycols 4000 to 20 000. Preferred plasticizers are tributyl citrate, triethyl citrate, acetyl triethyl citrate, dibutyl sebacate and diethyl sebacate. The amounts used are between 1 and 60, preferably 2 to 20, % by weight based on the film-forming polymer.

Multiparticulate pharmaceutical form

A further preferred embodiment is the multiparticulate pharmaceutical form described below.

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The multiparticulate pharmaceutical form brings about an advantageous, substantially uniform release of budesonide in the small intestine and in the large intestine and comprises at least two different types of pellets, one type of pellet releasing the active ingredient predominantly in the pH range of the small intestine and the other predominantly in the pH range of the large intestine.

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15 A suitable multiparticulate pharmaceutical form may comprise for example two forms of pellets A and B. The inner layer a) with the bound budesonide is present on a core, with pellet types A and B having two different polymer coatings, intermediate layers b), which determine the release of the active ingredient at different pH values.

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Pellet form A can be provided with a polymer coating which makes continuous release of active ingredient possible, and an outer coating which is resistant to gastric juice and which rapidly dissolves above approximately pH 5.5. The outer coating of pellet form A can be, for example, Eudragit® L 100-55.

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30 Pellet form B can be provided with a polymer coating, intermediate layer b), which in the USP release test at pH 6.8 releases less than 20% of the active ingredient in 6 hours and at pH 7.2 releases more than 50% of the active ingredient in 6 hours.

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The multiparticulate drug form may be in the form of a capsule filled with pellets, e.g. a gelatin capsule, or it may be a tablet in which the pellets have been

compressed together with conventional excipients to give the tablet unit.

5 The multiparticulate drug form is suitable for substantially uniform release of an active pharmaceutical ingredient in the small intestine and in the large intestine and comprises at least two forms of pellets, A and B, which comprise an active pharmaceutical ingredient in the core, but have different polymer
10 coatings which determine the release of the active ingredient at different pH values. In vitro, the USP release test (USP 23, method 2) results at pH 6.8 and at pH 7.2 in combined profiles which are between the individual release curves for the two pellet forms A
15 and B. In vivo, the release profile of pellet form A predominates in the small intestine, and release of active ingredient from pellet form B starts while in the large intestinal region.

20 The pellet cores consist entirely or partly of an active pharmaceutical ingredient. The cores are usually spherical or round and have diameters in the range from about 0.3 to 2 mm. The polymer coatings are in the range from about 2 to 16 mg of polymer per cm² surface
25 area of the cores.

Pellet form A

30 Pellet form A is provided with an inner polymer coating and an outer polymer coating.

Inner polymer coating

35 The inner polymer coating enables substantially pH-independent continuous release of active ingredient. The aim is an active ingredient release profile with which, in the USP release test (USP 23, method 2), at pH 6.8 there is about 40 to 70%, preferably 40 to 60%, release of active ingredient after 2 hours, and 60 to

100%, preferably 80 to 100% release after 4 hours. This is derived from the average residence time in the small intestine, which is about 4 hours.

5 The inner polymer coating of pellet form A may consist of a (meth)acrylate copolymer, of free-radical polymerized C1- to C4-alkyl esters of acrylic or methacrylic acid and (meth)acrylate monomers with a quaternary ammonium group in the alkyl radical.

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Appropriate (meth)acrylate copolymers are disclosed, for example, in EP-A 181 515 or DE patent 1 617 751. They are polymers which are soluble or swellable independently of the pH and which are suitable for
15 pharmaceutical coatings. A possible production process to be mentioned is bulk polymerization in the presence of a free-radical initiator dissolved in the monomer mixture. The polymer can likewise also be produced by a solution or precipitation polymerization. The polymer
20 can be obtained in this way in the form of a fine powder, which is achievable in the case of bulk polymerization by grinding, and in the case of solution and precipitation polymerization for example by spray drying.

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The (meth)acrylate copolymer is composed of 85 to 98% by weight free-radical polymerized C1- to C4-alkyl esters of acrylic or methacrylic acid and 15 to 2% by weight (meth)acrylate monomers with a quaternary
30 ammonium group in the alkyl radical.

Preferred C1- to C4-alkyl esters of acrylic or methacrylic acid are methyl acrylate, ethyl acrylate, butyl acrylate, butyl methacrylate and methyl methacrylate.

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The particularly preferred (meth)acrylate monomer with quaternary ammonium groups is 2-trimethylammoniummethyl methacrylate chloride.

A further suitable (meth)acrylate copolymer may be composed, for example, of 85 to less than 93% by weight C1- to C4-alkyl esters of acrylic or methacrylic acid and more than 7 to 15% by weight (meth)acrylate monomers with a quaternary ammonium group in the alkyl radical. Such (meth)acrylate monomers are commercially available and have been used for a long time for release-extending coatings (type Eudragit® RL).

10 A specifically suitable copolymer comprises, for example, 60% by weight methyl methacrylate, 30% by weight ethyl acrylate and 10% by weight 2-trimethylammoniummethyl methacrylate chloride (Eudragit® RL).

15 The desired release characteristics can be achieved for example through the thickness of the coating layer of polymer coatings of the "Eudragit® RL type" described above. This is achieved for example with a 5 to 15% coating of Eudragit® RL on active ingredient-containing
20 cores with a diameter of 0.8 to 1.2 mm. The required release characteristics can also be composed with other layer thicknesses by admixing a copolymer composed of 50-70% by weight methyl methacrylate, 20-40% by weight ethyl acrylate and 7-2% by weight 2-trimethylammoniummethyl methacrylate chloride ("Eudragit® RS
25 type"). A specifically suitable copolymer comprises 65% by weight methyl methacrylate, 30% by weight ethyl acrylate and 5% by weight 2-trimethylammoniummethyl methacrylate chloride be composed (Eudragit® RS). The
30 Eudragit® RL and RS types can be mixed for example in the ratios 10:1 to 1:10. Higher proportions of the "Eudragit® RL type" are preferred, e.g. 60 to 90% by weight in the mixture.

35 The inner polymer coating may also consist of a (meth)-acrylate copolymer composed of 20 to 40% by weight ethyl acrylate and 60 to 80% by weight methyl methacrylate, ethylcellulose or polyvinyl acetate.

Outer polymer coating

The outer polymer coating is a coating which is resistant to gastric juice and which rapidly dissolves only above about pH 5.5. The coating is thus intended to prevent release of active ingredient in the substantially stomach, i.e. this is intended to be no more than 10, preferably only 5, % according to USP 23. On transit into the small intestine it is intended that the outer polymer coating dissolve rapidly so that the release characteristics from this time onwards are determined by the inner polymer coating. If the outer polymer coating is too thin, too much active ingredient is released in the stomach. If the outer polymer coating is applied too thickly, it prevents direct release of active ingredient in the small intestine. Suitable layer thicknesses are, for example, in the range from 15 to 150 μm , preferably, for example, at 20 to 60 μm . Based on the weight of the core provided with the inner polymer coating and having a diameter of from 0.8 to 1.25 mm, it is usually suitable to apply polymer (based on dry matter) in the range from 8 to 40% by weight, preferably from 10 to 25% by weight.

The polymer coating which is resistant to gastric juice of pellet form A may be of a (meth)acrylate copolymer which contains acidic groups and has, for example, acrylic acid, but preferably methacrylic acid, residues.

The (meth)acrylate copolymer consists of 40 to 100, preferably 45 to 99, in particular 85 to 95, % by weight free-radical polymerized C_1 - to C_4 -alkyl esters of acrylic or methacrylic acid and may comprise 0 to 60, preferably 1 to 55, in particular 5 to 15, % by weight (meth)acrylate monomers with an anionic group in the alkyl radical.

C₁- to C₄-alkyl esters of acrylic or methacrylic acid are, in particular, methyl methacrylate, ethyl methacrylate, butyl methacrylate, methyl acrylate, ethyl acrylate and butyl acrylate.

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Suitable examples are also neutral (meth)acrylate copolymers of 20 to 40% by weight ethyl acrylate and 60 to 80% by weight methyl methacrylate (Eudragit[®] NE type) if they are used in a mixture with (meth)acrylate

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copolymers containing acidic groups.

Particularly suitable (meth)acrylate copolymers are composed of 40 to 60% by weight methacrylic acid and 60 to 40% by weight methyl methacrylate or 60 to 40% by

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weight ethyl acrylate (Eudragit[®] L or Eudragit[®] L100-55 types).

Also suitable in principle are anionic (meth)acrylate copolymers of 20 to 40% by weight methacrylic acid and

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80 to 60% by weight methyl methacrylate (Eudragit[®] S type).

Also suitable are (meth)acrylate copolymers consisting of 10 to 30% by weight methyl methacrylate, 50 to 70%

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by weight methyl acrylate and 5 to 15% by weight methacrylic acid (Eudragit[®] FS type).

The polymer coating which is resistant to gastric juice of pellet form A may also consist of shellac, HPMCP

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(hydroxypropylmethylcellulose phthalate), CAP (cellulose acetate phthalate), HPMC-AS (hydroxypropylmethylcellulose acetate succinate) or polyvinyl acetates phthalate.

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However, care must be taken in every case that the coating is adjusted for example in relation to layer thickness and, where appropriate, mixing with other polymers in such a way that it dissolves rapidly after transit into the small intestine.

Pellet form B

Pellet form B releases, at pH 6.8 in the USP release
5 test (USP 23, method 2), not more than 10%, preferably
not more than 5%, after 2 hours and not more than 20,
preferably not more than 10, % of the active ingredient
after 4 hours. At pH 7.2, about 40 to 60% of active
ingredient are released after 3 hours, and about 80 to
10 100 are released after 60 hours.

The polymer coating for pellet form B may be a (meth)-
acrylate copolymer which is composed of 60 to 95% by
weight free-radical polymerized C₁- to C₄-alkyl esters
15 of acrylic or methacrylic acid and 5 to 40% by weight
(meth)acrylate monomers with an acidic group in the
alkyl radical.

Particular suitable (meth)acrylate copolymers consist
20 of 10 to 30% by weight methyl methacrylate, 50 to 70%
by weight methyl acrylate and 5 to 15% by weight
methacrylic acid (Eudragit[®] FS type).

Likewise suitable are (meth)acrylate copolymers of 20
25 to 40% by weight methacrylic acid and 80 to 60% by
weight methyl methacrylate (Eudragit[®] S type).

Uses

30 The pharmaceutical formulation of the invention can be
used for the therapy of ulcerative colitis, Crohn's
disease and/or other, especially inflammatory, dis-
orders of the gastrointestinal tract which can be
treated with budesonide.

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Budesonide content per dose unit

The budesonide content, preferably micronized
budesonide, per dose unit (pellet) may be for example

from 0.5 to 30 mg, preferably 1 to 10 mg. A dose unit, a pellet-containing capsule or a tablet compressed from pellets, may comprise for example from 100 to 1000, preferably 150 to 750, pellets.

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EXAMPLES

The release test for budesonide is carried out in accordance with USP XXIII monograph <711> "Dissolution" with apparatus 2 (paddle) with 100 revolutions/min in phosphate buffer of pH 7.5 according to the monograph "Intestinal Fluid, Simulated, TS" without addition of pepsin or in purified water with the paddle at 100 revolutions/min with 500 ml of dissolving medium. 400 mg of sample were weighed for each determination. Detection took place by means of HPLC with a PP 18 column, 10 cm (Phenomenex) and UV detection at 246 nm. Equipment: pump L 7000 100 (from Merck-Hitachi, Darmstadt, Germany), autosampler L 7000 200 (from Merck-Hitachi, Darmstadt, Germany) UV/VIS detector L 4250 (from Merck-Hitachi, Darmstadt, Germany).

The volume injected was 100 µl, and the flow rate was 1 ml/min. The retention times averaged 2.5 min. At the end of the test, the pellets were homogenized with an Ultra Turrax for 10 min. The content was used as 100% value in the calculation. 3 to 6 tests were carried out for each medium.

Example 1 (not according to the invention): Determination of the rate of dissolution of budesonide without binder

The active ingredient dissolves under the stated conditions in vitro in the following way:

Time (min)	Release in purified water and phosphate buffer of pH 7.5 (% of theory)	
	Mean	Rel. standard deviation
0	0.0	0.0
60	ca. 3.7	0.4
120	ca. 5.4	1.0
180	ca. 7.1	1.6

Example 2 (according to the invention): Embedding of budesonide in a binder on the laboratory scale:

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6 g of budesonide, 5 g of talc and 1 g of triethyl citrate are dispersed in 65 of purified water using a homogenizer (Ultra Turrax, from Jahnke & Kunkel, Germany) and, while stirring gently with a propeller stirrer, mixed with 33 g of Eudragit® L 30 D-55. This spray suspension is sprayed onto 500 g of sucrose pellets, 0.8 × 1.0 mm (from Werner, Tornesch, Germany) while agitating in a STREA 1 fluidized bed apparatus (from Aeromatic, Bubendorf, Switzerland).

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15 The test is described by the following data:

Coating dry matter (CDM) [g]	10
Plasticizer based on CDM	10%
Release agent based on CDM	50%
Solids content of dispersion (m/m)	4.4%
CDM based on core mass	2%
Coating apparatus	Strea 1
Type of pellets	sucrose
Nozzle diameter [mm]	0.8
Spraying pressure [bar]	0.5
Batch size [g]	500
Amount applied [g]	110
Preheating time [min]	5
Spraying time [min]	52
Inlet air temperature [°C]	41
Outlet air temperature [°C]	30
Spraying rate [g/min]	2.1
After-drying time [min]	10

The pellets release the active ingredient under the indicated conditions in vitro as described below. At the end of the test, the pellets were homogenized using an Ultra Turrax for 10 min, and the budesonide concentration in the solution was again determined. The latter measurement was used as 100% value (theoretically possible budesonide content in the solution) in the calculation.

Time (min)	Release in phosphate buffer of pH 7.5 (% of theory)		Release in purified water (% of theory)	
	Mean	Rel. standard deviation	Mean	Rel. standard deviation
0	0.0	0.0	0.0	0.0
15	65.3	2.0	4.9	0.1
30	94.4	1.1	10.8	1.9
60	84.4	1.5	16.7	2.2
120	88.1	1.5	21.6	0.8

Example 3 (according to the invention): Embedding of budesonide in a binder on the pilot-plant scale:

36 g of budesonide, 60 g of talc and 12 g of triethyl citrate are dispersed in 632 of purified water using a homogenizer (Ultra Turrax, from Jahnke & Kunkel, Germany) and, while stirring gently with a propeller stirrer, mixed with 33 g of Eudragit® L 30 D-55. This spray suspension is sprayed onto 6000 g of sucrose pellets, 0.8 × 1.0 mm (from Werner, Tornesch, Germany) while agitating in a WSG 5 fluidized bed apparatus (from Glatt AG, Binzen, Germany).

The test is described by the following data:

Coating dry matter (CDM) [g]	120
Plasticizer based on CDM	10%
Release agent based on CDM	50%
Solids content of dispersion (m/m)	3.8%
CDM based on core mass	2%
Coating apparatus	WSG 5
Type of pellets	sucrose
Nozzle diameter [mm]	2.0
Spraying pressure [bar]	2.0
Batch size [g]	6000
Amount applied [g]	1140
Preheating time [min]	5
Spraying time [min]	57
Inlet air temperature [°C]	44
Outlet air temperature [°C]	34
Spraying rate [g/min]	20.0
After-drying time [min]	10

The pellets release the active ingredient under the indicated conditions in vitro in the following way:

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Time (min)	Release (% of theory)	
	Mean	Standard deviation
0	0.0	0.0
15	71.7	7.0
30	103.7	3.2
60	100.5	4.3
120	98.3	5.1

Example 4: Further processing of pellets from example 2 by application of a release-extending layer b) and of a layer c) resistant to gastric juice (pharmaceutical formulation or pharmaceutical form suitable for the therapy of ulcerative colitis)

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Preparation of spray suspension 1 (layer b)):

15 8.75 g of talc and 7 g of dibutyl sebacate are dispersed with a homogenizer (Ultra Turrax, from Jahnke & Kunkel, Germany) in 156.3 g of purified water and,

while stirring gently with a propeller stirrer, mixed with a mixture of 26.3 g of Eudragit® RS 30 D and 8.8 g of Eudragit® RL 30 D.

- 5 350 g of pellets from example 2 were coated in a Strea 1 fluidized bed apparatus (from Aeromatic, Bubendorf, Switzerland) under the following conditions:

Coating dry matter (CDM) [g]	35
Plasticizer based on CDM	20%
Release agent based on CDM	50%
Solids content of dispersion (m/m)	17%
CDM based on core mass	10%
Coating apparatus	Strea 1
Type of pellets	example 2
Nozzle diameter [mm]	0.8
Spraying pressure [bar]	0.5
Batch size [g]	350
Amount applied [g]	297.5
Preheating time [min]	5
Spraying time [min]	117
Inlet air temperature [°C]	40
Outlet air temperature [°C]	329
Spraying rate [g/min]	2.5
After-drying time [min]	5

- 10 The coated cores then undergo after-drying on trays in a mechanical convection oven at 40°C for 24 h.

Preparation of spray suspension 2 (layer c)):

- 15 1.3 g of glycerol monostearate, 1.3 g of triethyl citrate and 0.5 g of polysorbate 80 are dispersed in 156.3 g of purified water using a homogenizer (Ultra Turrax, from Jahnke & Kunkel, Germany) and, while stirring gently with a propeller stirrer, mixed with
20 87.5 g of Eudragit® FS 30 D.

- 400 g of pellets from example 2 with a release-slowing coating of spray suspension 1 were coated in a Strea 1 fluidized bed apparatus (from Aeromatic, Bubendorf, Switzerland) under the following conditions:
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Coating dry matter (CDM) [g]	30
Plasticizer based on CDM	3%
Release agent based on CDM	5%
Solids content of dispersion (m/m)	20%
CDM based on core mass	7.5%
Coating apparatus	Strea 1
Type of pellets	example 2
Nozzle diameter [mm]	0.8
Spraying pressure [bar]	0.5
Batch size [g]	400
Amount applied [g]	165
Preheating time [min]	5
Spraying time [min]	54
Inlet air temperature [°C]	31
Outlet air temperature [°C]	25
Spraying rate [g/min]	3.1
After-drying time [min]	5

The coated cores then undergo after-drying on trays in a mechanical convection oven at 40°C for 2 h.

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The pellets coated with layers b) and c) release the active ingredient under the indicated conditions in vitro in the following way:

Time (min)	Release in phosphate buffer of pH 7.5 (% of theory)	
	Mean	Rel. standard deviation
0	0.0	0
30	0.0	0
60	0.0	0
120	1.8	0.1
180	4.2	0.3
240	11.7	1.8
300	32.6	2.0
360	50.5	7.4
480	73.3	7.0
600	85.3	3.0